COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, **Nicholas Kim Hayward** of The Human Genetics Laboratory, Queensland Institute of Medical Research, Herston, QLD 4029, Australia, a research scientist, declare as follows:

1.1. I have been asked by the Patent Attorneys representing Human Genome Sciences ("HGS") to serve as a scientific consultant in connection with the Ludwig Institute for Cancer Research Opposition to the issuance of HGS Australian Patent Application 696764, in the name of HGS, entitled: "Vascular Endothelial Growth Factor-2" ("the HGS patent specification").

1.2. In acting as a scientific consultant for HGS, I provided a Statutory Declaration executed December 8, 2000 ("Hayward Declaration 1") in connection with the Opposition of the HGS patent specification, in which I provided my comments and opinions on what the HGS patent specification would have disclosed and described to me as a researcher working in the field of the molecular biology of growth factors in Australia in March 1994, which I understand is the earliest

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priority date of the HGS patent specification. I also provided comments and opinions on the experimental evidence provided in Dr. Alitalo's Statutory Declaration executed on 15 February 2000 ("Alitalo Declaration 1").

Alitalo Declaration 2

1.3. I have been asked by the Patent Attorneys representing HGS to review and provide my comments and opinions on the Statutory Declaration executed by Dr. Alitalo on 14 September 2001 ("Alitalo Declaration 2").

1.4. When I read VEGF-2 in the HGS patent specification I understood it to be referring to VEGF-C. These names are alternate nomenclature for the same protein.

New experiments presented in Alitalo Declaration 2

1.5. The new experiments presented in Alitalo Declaration 2 are flawed for the following reasons:

- Dr Alitalo does not take account of all of the information presented in the HGS patent specification. None of his experiments report on the effect of attaching a heterologous signal sequence to the 350 amino acid VEGF-2 sequence. This is discussed more fully in paragraph 1.7 below.
- Dr. Alitalo does not provide appropriate positive and negative controls for the expression experiments.
- No experiments were conducted nor were results produced concerning the transfection efficiency of the plasmids used in the experiments. The transfection efficiency will directly correlate with the level of protein expression detected.
- No data is presented concerning parameters such as cell densities or growth conditions all of which can affect the transfection efficiency of expression constructs into cells.
- The experimental protocol described in Alitalo Declaration 2 does not allow for detection of VEGF-2 protein expression over various time points. Rather, protein levels are assessed fifty hours post-transfection (forty-eight hours and overnight metabolic labelling). Without measuring for VEGF-2 expression over various time points, it is not possible to detect

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VEGF-2 that has been expressed and purportedly degraded over time.

Consequently, Dr Alitalo's experiments do not, in my opinion provide any meaningful conclusions regarding the expression, processing and secretion of VEGF-2 as disclosed in the HGS patent specification.

1.6. In designing new experiments, Dr Alitalo seems to have ignored the fact that the HGS patent specification clearly discloses the utilisation of a heterologous signal sequence capable of directing secretion of the translated protein (see, the HGS patent specification at page 14, lines 6-23). Further, in designing these identified experiments Dr Alitalo seems to have completely ignored my comments in Hayward Declaration 1 (see for example paragraph 3.19) where I emphasised that the use of a heterologous signal sequence in the production of VEGF-2 is something I ***could*** and ***would*** have attempted in March 1994 had the VEGF-2 sequence reported in the HGS patent specification not been secreted following properly controlled expression experiments. Nothing in Alitalo Declaration 2 has led me to change this opinion. In my opinion the HGS patent specification provides all of the information that I would have required to produce VEGF-2 in its mature form.

Paragraphs 3.7 and 5.5

1.7. In paragraphs 3.7 and 5.5 of Alitalo Declaration 2, Dr Alitalo appears to me to suggest that one would not expect to achieve processing of the 350 amino acid sequence disclosed in the HGS patent specification. The processing of a protein such as VEGF-2 is determined by its amino acid sequence. In the absence of any evidence to the contrary I would have proceeded in March 1994 on the basis that the 350 amino acid sequence of VEGF-2 contained all the necessary information and signals required by a host cell to process the amino acid sequence to its mature form. By March 1994 I was aware that any given host cell would possess the proteolytic enzymes and cellular machinery to naturally process a protein such as VEGF-2 to its mature form. I was also aware that post translational processing of an amino acid sequence is a natural and inherent property of the expression and secretion of a protein from a host cell.

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Paragraphs 4.1 to 4.3

1.8. In paragraphs 4.1 to 4.3 of Alitalo Declaration 2, Dr Alitalo alleges that the VEGF-2 clone deposited with the American Type Culture Collection as ATCC Accession Number 75698 does not contain the complete 350 amino acid sequence when compared to the sequence set forth in Figure 1 of the HGS patent specification. Had I been presented with the HGS patent specification in March 1994, I would not have needed the deposit to isolate the 350 amino acid coding sequences for VEGF-2. Rather, I would have isolated the sequence from a suitable library (such as that mentioned in the HGS patent specification at page 5, lines 19-26) or from RNA from the sources provided by the HGS patent specification (page 5, lines 19-24, Example 1 and Figure 5) using the information in Figure 1 of the HGS patent specification. By March 1994 techniques such as PCR, were routinely available for achieving this objective and were commonly used in my laboratory for isolating nucleotide sequences. An additional approach would be to synthesize a double stranded oligonucleotide containing the missing sequence and ligate the oligonucleotide to the DNA obtained from the ATCC deposit. Such research was entirely routine by March 1994. Thus, in my opinion, the information that I would have relied upon to isolate the 350 amino acid sequence is that derived from Figure 1 in the HGS patent specification, which would have been sufficient for me or other skilled molecular biologists to isolate the sequence.

Paragraph 5.6

1.9. In paragraph 5.6 of Alitalo Declaration 2, Dr Alitalo mentions for the first time that the HGS patent specification does not disclose the molecular weight of the mature form of VEGF-2. Neither I nor my colleagues who were working with PDGF/VEGF family members in Australia in March 1994 would have required this information from the HGS patent specification to produce and recognize a mature form of the protein. Regardless, using the HGS patent specification I and I believe my colleagues could have easily expressed and secreted the protein and then measured the molecular weight of the secreted and processed forms of the protein. Had we done this, we would have identified the molecular weight of the mature form of VEGF-2, as the

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molecular weight is an intrinsic and natural property of the processing of the protein. The gathering of such information was an entirely routine practice for molecular biologists in Australia by March 1994.

1.10. In paragraph 5.6 of Alitalo Declaration 2, Dr Alitalo suggests that the experiments reported by Dr Powers should be ignored because they are "unrelated" to the teachings in the HGS patent specification. In reaching this conclusion, Dr Alitalo seems to have ignored the fact that the HGS patent specification clearly discloses the utilisation of a heterologous signal sequence capable of directing secretion of the translated protein (see, the patent specification at page 14, lines 6-23). I have been presented with a copy of (a) Susan Powers Declaration dated 13 December 2000 ("Power Declaration 1") and (b) Susan Powers Declaration dated 22 March 2002 ("Power Declaration 2") and note that they both demonstrate that a 350 amino acid form of VEGF-2 could be expressed, processed and secreted. The methodology used to carry out the experiments described and performed by Dr Powers in both Power Declaration 1 and Power Declaration 2 are, in my opinion, the types of experiments that I and I believe any molecular biologist of ordinary skill in Australia would have performed in March 1994, when presented with the patent specification.

Aaronson Declaration 2

1.11. The Patent Attorneys representing HGS have also presented to me a second Declaration by Professor Stuart Aaronson dated 22 March 2002 ("Aaronson Declaration 2") commenting, *inter alia*, on Alitalo Declaration 2. I have read and understood Aaronson Declaration 2 and its annexed documents.

1.12. My separate comments and observations concerning Alitalo Declaration 2 are provided above. These comments and observations are, I believe, consistent with those made by Professor Aaronson in Aaronson Declaration 2. Thus, I am in complete agreement with the opinions expressed by Professor Aaronson in his Declaration.

AND I make this solemn declaration by virtue of the Statutory Declarations Act, 1959 and subject to the penalties provided by that Act for the making of

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false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DATED this day Twenty Sixth of March 2002.

DECLARED at: Brisbane, Queensland)
BEFORE me: NERIDA FOX)

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N. Hayward
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Nicholas Kim Hayward

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